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EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
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1644

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/833,526

Applicant(s)

HORWITZ, DAVID A.

Examiner

Phuong Huynh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 04 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 4-8 is/are pending in the application.
- 4a) Of the above claim(s) None is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 4-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/4/03 has been entered.
2. Claims 4-8 are pending and are being acted upon in this Office Action.
3. Claims 4-7 are objected to because "A" should have been "The" for all dependent claims that depend from independent claim 8.
4. Claim 8 is objected to because "PMBCs" should have been "PBMCs" which stands for peripheral blood mononuclear cells.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:  

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 4-8 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**  

The recitation of "PMBCs", in claim 8 has no support in the specification as filed. The specification discloses "PBMCs", which stands for peripheral blood mononuclear cells on page 9 instead of "PMBCs". Applicants have not pointed the support for said phrase.
7. The following is a quotation of the second paragraph of 35 U.S.C. 112:  

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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8. Claims 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "combining *ex vivo* said recipient PMBCs" in claim 8 is indefinite and ambiguous because the specification discloses only CD4+ T cells, instead of PMBCs, from the recipient are cultured with T cell-depleted mononuclear cells from the donor in the presence of TGF- $\beta$ . The recipient CD4+ cells which reacts with donor alloantigens in the presence of TGF- $\beta$  for ten days to become suppressor T cells. Applicants have not pointed the support for said phrase. Correction is required.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 8, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48524 publication (of record, Sept 1999, PTO 892) in view of Rosario *et al* (Blood 93(10): 3558-3564, May 1999; PTO 892) and Garderet *et al* (of record, Transplantation 67(1): 124-30; Jan 1999; PTO 892).

The WO 99/48524 publication teaches a method to decrease graft rejection by inducing T cell tolerance *ex vivo* wherein the reference method comprises isolating peripheral mononuclear blood cells (PMBCs) from a donor and a recipient, depleting T cell from the recipient PMBC by enriched one or more cell types antibodies such as CD8+ T cells, CD4+ Cells (See page 12, lines 15-22, in particular), irradiate the recipient PMBCs to render them non-proliferative and cannot attack the donor cells but still stimulate the donor cells to become tolerant to the recipient cells (See page 18, lines 10-16, See claims of WO99/48524, page 14, lines 12-15, in particular), treating the reference PMBCs with a regulatory composition such as TGF- $\beta$  (See page 7, line 1-2, page 13, line 8-9, page 14, line 2-7, in particular) or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 (see page 14, lines 8-10, in particular). After expanding said cells in culture, the reference donor cells are transferred to the recipient (See page 24, lines 1-3, see claim 5 of WO99/48524, in

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particular). The reference method further enriched for CD8+ T cells (See page 12, lines 22-23, in particular). The WO 99/48524 publication teaches that treating donor cells with a regulatory composition such as TGF- $\beta$  (See page 7, line 1-2, page 13, line 8-9, page 14, line 2-7, in particular) or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 (see page 14, lines 8-10, in particular) can activate donor regulatory cells such as CD8+ T cells to block immune attack against the recipient cells (See page 10, lines 8-9, in particular) and thereby inducing tolerance in the donor cells to recipient tissue to avoid Graft versus Host Disease (GVHD) in patients (See Abstract, in particular).

The claimed invention as recited in claim 8 differs from the teachings of the reference only that the method wherein T cell-depleted mononuclear cells from said organ donor PMBCs are irradiated instead of irradiated recipient PMBC cells.

Rosario *et al* teach UVC and UVB could induce humoral immune tolerance to allogenic MHC antigens by increase in Th2 cytokine level such as IL4 and IL5 and a lower level of gamma interferon (See page 3558, column 2, page 3564, in particular). Rosario *et al* teach that recipient BALB/c mice transplanted with PMB and spleen MNL from tolerant CBA donors has better overall survival and attenuated Graft versus host disease (See abstract, in particular). The reference method of induction of immune tolerance in donor CBA mice is by transfusion of UVB irradiated (MNL) BLA/c (H-2<sup>d</sup>) peripheral blood mononuclear leukocytes (MNL) into CBA/HT6 (H-2k) mice, bone marrow cells and spleen MNL from tolerant or naïve CBA mice are transplanted into lethally irradiated BALB/c mice (abstract, page 3559, column 1, in particular). The reference method wherein the recipient BALB/c mice transplanted with tolerant CBA donor BMC and spleen MNL cells had lower serum levels of  $\gamma$ FN and higher IL-4 than naïve CBA donor mice after bone marrow transplant (See page 3559, column 1, page 3562, column 1, T-cell cytokine response after BMT, in particular). Rosario *et al* further teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the grafts; T-cell depletion from marrow graft has been successfully applied to prevent graft rejection caused by GVHD (See page 3558, Introduction, in particular) and moderate to severe GVHD can be induced by including 2.5 to 4 x 10<sup>5</sup> donor spleen MNL with T cell deficient bone marrow cells (See page 3560, column 1, GVHD after transplantation with bone marrow and spleen cells from tolerant donor, in particular). Rosario *et al* teach that cellular immune tolerance by irradiation that is associated

with an increase in Th2 cytokine level such as IL4 and IL5 and a lower level of gamma interferon (See page 3564, in particular).

Garderet *et al* teach a method of depleting alloreactive lymphocytes of donor from peripheral blood mononuclear cell preparation to reduce graft versus host disease (graft rejection). The reference method comprises treating PMBC cells with irradiated peripheral blood mononuclear cell from recipient and expand said cell in culture (See abstract, in particular). The reference further teaches selective enrichment of CD4+ T cells and depletion of host specific alloreactive CD4+ T cell. The advantage of depleting alloreactive lymphocytes of donor peripheral blood mononuclear cell preparation prevents graft versus host disease graft rejection due to specific cytotoxic activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to decrease graft rejection by isolating peripheral mononuclear blood cells as taught by the WO 99/48524 publication, Rosario *et al* and Garderet *et al*, irradiating T cell-depleted monoclonal cells from donor PMBCs as taught by Rosario *et al*, combining ex vivo the recipient PMBCs with the donor irradiated T cell-depleted mononuclear cells with a regulatory composition such as TGF $\beta$  or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 as taught by the WO 99/48524 publication, expanding the recipient suppressor T cells and administering said recipient suppressor T cells into the recipient as taught by the WO 99/48524 publication and Garderet *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Rosario *et al* teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the marrow grafts; T-cell depletion from marrow graft has been successfully applied to prevent GVHD (See page 3558, Introduction, in particular) and irradiated peripheral blood mononuclear leukocytes have been shown to induce humoral immune tolerance to alloantigen (See abstract, in particular). The WO 99/48524 publication teaches that treating donor cells with a regulatory composition such as TGF- $\beta$  (See page 7, line 1-2, page 13, line 8-9, page 14, line 2-7, in particular) or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 (see page 14, lines 8-10, in particular) can activate donor regulatory cells such as CD8+ T cells to block immune

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attack against the recipient cells (See page 10, liens 8-9, in particular) and thereby inducing tolerance in the donor cells to recipient tissue to avoid Graft versus Host Disease (GVHD) in patients (See Abstract, in particular). Garderet *et al* teach co-culturing irradiated T cell depleted monoclonal cells from donor or recipient inhibits host specific cytotoxic activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular). The term "comprising" is open-ended. It expands the claimed regulatory composition to include additional compound to read on the reference regulatory composition as taught by Horwitz *et al*. The recitation of PMBCs from recipient are enriched for CD4+ T cells in claim 5 is an obvious variation of PMBCs from donor are enriched for CD4+ T cells as taught by the WO 99/48524 publication.

Applicants' arguments filed 3/4/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Horwitz does not teach the method wherein the recipient PBMCs are combined with a population of **irradiated donor T cells depleted mononuclear cells** of instant application. (2) Horwitz teaches **irradiated recipient PMBC cells** instead of irradiated donor PMBCs to induce a population of donor suppressor T cells. (3) Garderet *et al* does not teach or disclose a method comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells.

However, the recitation of irradiated **donor mononuclear cell (PMBC)** depleted of T cells is an obvious variation of the irradiated **recipient PMBC cells** as taught by Horwitz *et al*. Further, Rosario *et al* teach UVC and UVB could induce humoral immune tolerance to allogenic MHC antigens (See page 3558, column 2, in particular). Rosario *et al* teach that recipient BALB/c mice transplanted with PMBCs and spleen MNL from tolerant CBA donors has better overall survival and attenuated Graft versus host disease (See abstract, in particular). Rosario *et al* teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the marrow grafts; T-cell depletion from marrow graft has been successfully applied to prevent GVHD (See page 3558, Introduction, in particular). Garderet *et al* teach co-culturing irradiated T cell depleted monoclonal cells from donor or recipient inhibits host specific cytotoxic activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular). It would have been obvious to one of ordinary skill in the art at the time the invention was made to decrease graft rejection by isolating

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peripheral mononuclear blood cells as taught by the WO 99/48524 publication, Rosario *et al* and Garderet *et al*, irradiating T cell-depleted monoclonal cells from recipient or donor PMBCs with UVC and UVB to induce humoral immune tolerance to allogenic MHC antigens as taught by Rosario *et al* or Horwitz *et al*, combining ex vivo the recipient PMBCs with the donor irradiated T cell-depleted mononuclear cells with a regulatory composition such as TGF $\beta$  or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 as taught by the WO 99/48524 publication, expanding the recipient suppressor T cells and administering said recipient suppressor T cells into the recipient as taught by the WO 99/48524 publication and Garderet *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Rosario *et al* teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the grafts; T-cell depletion from marrow graft has been successfully applied to prevent graft rejection caused by GVHD (See page 3558, Introduction, in particular) and UVC and UVB could induce humoral immune tolerance to allogenic MHC antigens by increase in Th2 cytokine level such as IL4 and IL5 and a lower level of gamma interferon (See page 3558, column 2, page 3564, in particular). The WO 99/48524 publication teaches that treating donor cells with a regulatory composition such as TGF- $\beta$  (See page 7, line 1-2, page 13, line 8-9, page 14, line 2-7, in particular) or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 (see page 14, lines 8-10, in particular) can activate donor regulatory cells such as CD8+ T cells to block immune attack against the recipient cells (See page 10, lines 8-9, in particular) and thereby inducing tolerance in the donor cells to recipient tissue to avoid Graft versus Host Disease (GVHD) in patients (See Abstract, in particular). Garderet *et al* teach co-culturing irradiated T cell depleted monoclonal cells from donor and recipient inhibits host specific cytotoxic activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular).

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11. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48524 publication (of record, Sept 1999, PTO 892) in view of Rosario *et al* (Blood 93(10): 3558-3564, May 1999; PTO 892) and Garderet *et al* (of record, Transplantation 67(1): 124-30; Jan 1999; PTO 892) as applied to claims 8, 5 and 7 mentioned above and further in view of Bonig *et al* (of record, Scand J Immunol 50: 612-618, Dec 1999; PTO 892) or Dooks *et al* (Abstract, European Cytokine Network 9(3): 169; 1998; PTO 1449).

The combined teachings of WO 99/48524 publication, Rosario *et al* and Garderet *et al* have been discussed supra.

The claimed invention in claim 4 differs from the combined teachings of the references only that the method for decreasing grafts rejection wherein the regulatory composition further comprises cytokine selected from the group consisting of IL-2 and IL-15.

Bonig *et al* teach IL-15 has some functional similarities to IL-2 since they share a common signal transduction pathway (See page 612, column 1, first paragraph, in particular) and addition of TGF- $\beta$ , which is a potent suppressor of T cell proliferation, to T cell culture in vitro in the presence of IL-15 or IL-2 further inhibits IFN $\gamma$  production mediated by either IL-15 or IL-2 alone (See page 615, Figs 2C and 2E, Fig 3, Table 1, in particular). Bonig *et al* teach that a combination of TGF- $\beta$  and IL-15 or IL-2 induces T cell anergy (tolerance) by reducing the number of IFN- $\gamma$ /CD4  $+/+$  and IFN- $\gamma$ /CD8  $+/+$  cells by 50% and reduces cytoplasmic interferon-accumulation equally in CD4 $+$  and CD8 $+$  cells (See Table 1, in particular).

Dooks *et al* teach that IL-2 pretreatment sensitizes T cells for Fas/Apo-1 apoptosis whereas IL-15 pretreatment induces T cell anergy (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the TGF $\beta$  as taught by the WO 99/48524 publication with the IL-15 or IL-2 as taught by Bonig *et al* and Dooks *et al* for a method of reducing graft rejection by induction of T cell tolerance (anergy) ex vivo as taught by the WO 99/48524 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to this because Bonig *et al* teach that a combination of TGF- $\beta$  and IL-15 or IL-2 induces T cell anergy (tolerance) by reducing the number of IFN- $\gamma$ /CD4  $+/+$  and IFN- $\gamma$ /CD8  $+/+$  cells by 50% and reducing cytoplasmic interferon-accumulation equally in CD4 $+$  and CD8 $+$  cells (See Table 1, in particular). Dooks *et al* teach IL-2 pretreatment sensitizes T cells for Fas/Apo-1 apoptosis

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whereas IL-15 pretreatment induces T cell anergy (See abstract, in particular). Rosario *et al* teach that cellular immune tolerance by irradiation that is associated with an increase in Th2 cytokine level such as IL4 and IL5 and a lower level of gamma interferon (See page 3564, in particular). Rosario *et al* further teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the marrow grafts; T-cell depletion from marrow graft has been successfully applied to prevent GVHD (See page 3558, Introduction, in particular).

Applicants' arguments filed 3/4/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Horwitz does not teach the method wherein the recipient PBMCs are combined with a population of **irradiated donor T cells depleted mononuclear cells** of instant application. (2) Horwitz teaches **irradiated recipient PMBC cells** instead of irradiated donor PMBCs to induce a population of donor suppressor T cells. Garderet *et al* does not teach or disclose a method comprising incubating recipient PBMCs with a population of irradiated donor T cell-depleted mononuclear cells. (3) Garderet *et al* does not teach a method or disclose a method comprising incubating recipient PMBCs with a population of irradiated donor T cell-depleted mononuclear cells. (4) Bonig *et al* does not teach or disclose a method comprising incubating recipient PBMCs with a population of donor irradiated T cell-depleted mononuclear cells.

However, the recitation of **irradiated donor mononuclear cell (PMBC) depleted of T cells** is an obvious variation of the **irradiated recipient PMBC cells** as taught by Horwitz *et al*. Further, Rosario *et al* teach that cellular immune tolerance by irradiation that is associated with an increase in Th2 cytokine level such as IL4 and IL5 and a lower level of gamma interferon (See page 3564, in particular). Rosario *et al* teach that recipient BALB/c mice transplanted with PMBCs and spleen MNL from tolerant CBA donors has better overall survival and attenuated Graft versus host disease (See abstract, in particular). Rosario *et al* further teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the marrow grafts; T-cell depletion from marrow graft has been successfully applied to prevent GVHD (See page 3558, Introduction, in particular). Garderet *et al* teach co-culturing irradiated T cell depleted monoclonal cells from donor or recipient inhibits host specific cytotoxic activity and allows therapeutic infusion

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(reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to decrease graft rejection by isolating peripheral mononuclear blood cells as taught by the WO 99/48524 publication, Rosario *et al* and Garderet *et al*, irradiating T cell-depleted monoclonal cells from recipient or donor PMBCs with UVC and UVB to induce humoral immune tolerance to allogenic MHC antigens as taught by Rosario *et al* or Horwitz *et al*, combining ex vivo the recipient PMBCs with the donor or recipient irradiated T cell-depleted mononuclear cells with a regulatory composition such as TGF $\beta$  or TGF- $\beta$ , IL-10 and IL-2 or TGF- $\beta$  and IL-10 as taught by the WO 99/48524 publication or a combination of TGF- $\beta$  and IL-15 or IL-2 as taught by Bonig *et al* or Doms *et al*, expanding the recipient suppressor T cells and administering said recipient suppressor T cells into the recipient as taught by the WO 99/48524 publication and Garderet *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the TGF $\beta$  as taught by the WO 99/48524 publication with the IL-15 or IL-2 as taught by Bonig *et al* and Doms *et al* for a method of reducing graft rejection by induction of T cell tolerance (anergy) ex vivo as taught by the WO 99/48524 publication because Bonig *et al* teach that a combination of TGF- $\beta$  and IL-15 or IL-2 induces T cell anergy (tolerance) by reducing the number of IFN- $\gamma$ /CD4 +/+ and IFN- $\gamma$ /CD8 +/+ cells by 50% and reducing cytoplasmic interferon-accumulation equally in CD4+ and CD8+ cells (See Table 1, in particular). Doms *et al* teach IL-2 pretreatment sensitizes T cells for Fas/Apo-1 apoptosis whereas IL-15 pretreatment induces T cell anergy (See abstract, in particular).

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over of WO 99/48524 publication (of record, Sept 1999, PTO 892) in view of Rosario *et al* (Blood 93(10): 3558-3564, May 1999; PTO 892) and Garderet *et al* (of record, Transplantation 67(1): 124-30; Jan 1999; PTO 892) as applied to claims 8, 5 and 7 mentioned above and further in view of Early *et al* (of record, Clin Exp Immunol 116(3): 527-33, June 1999; PTO 892), Heitger *et al* (of record, Blood 90(2): 850-57, July 1997; PTO 892) and Chen *et al* (of record, J Immunology 161: 909-918, 1998; PTO 892).

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The combined teachings of WO 99/48524 publication, Rosario *et al* and Garderet *et al* have been discussed supra.

The claimed invention in claim 6 differs from the combined teachings of the references only that the method for decreasing graft rejection wherein said CD4+ cells are enriched for naïve CD4+ T cells.

Early *et al* teach a method of enriching for naïve CD4+ T cells for reducing the incidence of graft versus host disease (See abstract, in particular). The reference shows that CD4+ CD45RA+ naïve T cells from human cord blood can transform more quickly than their adult counterpart into functionally equivalent CD4+CD45RO+ (memory) T cells.

Heitger *et al* teach CD45 isotype has been linked to different cell functions such as CD4+/CD45RA+ (naïve) T cells acting as suppressor/inducer cells whereas CD4+/CD45RO+ (memory) T cells acting as helper/inducer cells (See page 850, column 1, in particular).

Chen *et al* teach CD45 specific T cell plays a role in graft versus host disease (See entire document, page 912, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to enrich CD4+ CD45RA+ naïve T cells from either donor or recipient as taught by Early *et al*, Heitger *et al* and Chen *et al* for a method to decrease graft rejection as taught by the WO 99/48524 publication, Rosario *et al* and Garderet *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Chen *et al* teach CD45 specific T cell plays a role in graft versus host disease (See entire document, page 912, column 1, in particular). Heitger *et al* teach CD45 isotype has been linked to different cell functions such as CD4+/CD45RA+ (naïve) T cells acting as suppressor/inducer cells whereas CD4+/CD45RO+ (memory) T cells acting as helper/inducer cells (See page 850, column 1, in particular). Early *et al* teach enriching for naïve CD4+ T cells could reducing the incidence of graft versus host disease (See abstract, in particular).

Applicants' arguments filed 3/4/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Early *et al* does not teach a method for enriching naïve CD4+ T cells for reducing the incidence of GVHD and a method to decrease organ rejection comprising incubating recipient PMBCs with a population of irradiated donor T cell-dependent

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mononuclear cells. (2) Heitger *et al* does not teach a method to decrease organ rejection comprising incubating recipient PMBCs with a population of irradiated donor T cell-depleted mononuclear cells. (3) Chen *et al* does not teach a method to decrease organ rejection comprising incubating recipient PMBCs with a population of irradiated donor T cell-depleted mononuclear cells.

However, Early *et al* teach a method of enriching for naïve CD4+ T cells for reducing the incidence of graft versus host disease (See abstract, in particular). The reference shows that CD4+ CD45RA+ naïve T cells from human cord blood can transform more quickly than their adult counterpart into functionally equivalent CD4+CD45RO+ (memory) T cells. Heitger *et al* teach CD45 isotype has been linked to different cell functions such as CD4+/CD45RA+ (naïve) T cells acting as suppressor/inducer cells whereas CD4+/CD45RO+ (memory) T cells acting as helper/inducer cells (See page 850, column 1, in particular). Chen *et al* teach CD45 specific T cell plays a role in graft versus host disease (See entire document, page 912, column 1, in particular). The claimed invention in claim 6 differs from the combined teachings of the references only that the method for decreasing graft rejection wherein said CD4+ cells are enriched for naïve CD4+ T cells. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to enrich CD4+ CD45RA+ naïve T cells from either donor or recipient as taught by Early *et al*, Heitger *et al* and Chen *et al* for a method to decrease graft rejection as taught by the WO 99/48524 publication, Rosario *et al* and Garderet *et al*.

The recitation of irradiated donor mononuclear cell (PMBC) depleted of T cells is an obvious variation of the irradiated recipient PMBC cells as taught by Horwitz *et al*. Further, Rosario *et al* teach UVC and UVB could induce humoral immune tolerance to allogenic MHC antigens (See page 3558, column 2, in particular). Rosario *et al* teach that cellular immune tolerance by irradiation that is associated with an increase in Th2 cytokine level such as IL4 and IL5 and a lower level of gamma interferon (See page 3564, in particular). Rosario *et al* teach that recipient BALB/c mice transplanted with PMBCs and spleen MNL from tolerant CBA donors has better overall survival and attenuated Graft versus host disease (See abstract, in particular). Rosario *et al* further teach that the severity of GVHD is related to the degree of difference between host and donors across the major histocompatibility barrier and the presence of donor T cells in the marrow grafts; T-cell depletion from marrow graft has been successfully applied to prevent GVHD (See page 3558, Introduction, in particular). Garderet *et al* teach co-culturing irradiated T cell depleted monoclonal cells from donor or recipient inhibits host specific cytotoxic

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activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular).


13. No claim is allowed.
14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner

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May 5, 2003

  
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